PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100829-1 WO	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE 03/01399	International filing date *(day/month/year)* 08.09.2003	Priority date *(day/month/year)* 09.09.2002
International Patent Classification (IPC) or both national classification and IPC C07D211/22		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.03.2004	25.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Usuelli, A Telephone No. +49 89 2399-7366

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE 03/01399

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-42 as published

Claims, Numbers

1-11 as published

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-5,8,9 all in part

   because:

   ☒ the said international application, or the said claims Nos. 8-10 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-5,8,9 all in part

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7,11
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Claims 8-10 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims, cf. Article 34(4)(a)(I) PCT.

2- This international preliminary examination is limited to those parts of the application for which a search report has been established, Rule 66.1 (e) PCT (Cf. Boxes I:1 and I:2 of the international search report).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1- Reference is made to the following documents:

d1: GB-A-2 347 423A
d2: J. MED. CHEM. vol. 38, 1995, pages 1264 - 1266
d3: J. MED. CHEM. vol. 41, 1998, pages 4623 - 4635
d4: WO 95 19344 A1
d5: WO 94 10165 A1
d6: BIOORGANIC & MEDICINAL CHEMISTRY LETTERS vol. 12, no. 13, 08 July 2002, pages 1755 - 1758
d7: BIOORGANIC & MEDICINAL CHEMISTRY LETTERS vol. 12, no. 2, 2002, pages 261 - 264

2- Novelty

Present compounds of formula (I) differ from the compounds cited in d1 to d7 mainly on account of the naphthyl ring.

Since all the claims relate to the compounds of formula (I), the requirements of Art. 33.2 are met.

3- Inventive activity

3.1- The applicant seems to have set himself the task of providing compounds having a dual activity as NK1 antagonists and serotonin reuptake inhibitors. These compounds

can be used for the treatment of various diseases such as hypertension and depression.
Documents d1 and d7 relate to piperidine derivative having the same pharmacological activity of present compounds. Considering the chemical structures of the compounds disclosed in these documents, it is considered that d1 represent the closest state of the art.
The tests disclosed from pages 12 to 16 of the present application show the activity of the compound A of the present invention in the SERT binding assay and in the NK1 FLIPR assay.
For the purpose of assessing the inventive activity during the international phase, it is accepted that substantially all the claimed compounds are NK1 antagonists and serotonin reuptake inhibitors.
The objective technical problem can therefore be seen in the provision of further agents having a dual activity as NK1 antagonists and serotonin reuptake inhibitors.

3.2- As indicated above, present compounds differ from the compounds of d1 in view of the naphthalene ring. Additionally, in the compounds of d1 the piperidine is substituted in position 1 by a hydroxy-substituted phenylalkyl moiety which is not included in the definition of present group R3.
The relevant compounds of d7 (8-13) have a different substituent in the position 4 of the piperidine and do not contain a naphthalene ring.
Taking into account of these structural differences, it appears that the skilled person faced with the technical problem defined above, would not arrive to the present compounds in an obvious manner.